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Patentanmeldung Nr. Patent application No. Demande de brevet n°

04075003.6

Der Präsident des Europäischen Patentamts;  
Im Auftrag

For the President of the European Patent Office  
Le Président de l'Office européen des brevets  
p.o.

R C van Dijk



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Bezeichnung der Erfindung/Title of the invention/Titre de l'invention:  
(Falls die Bezeichnung der Erfindung nicht angegeben ist, siehe Beschreibung.  
If no title is shown please refer to the description.  
Si aucun titre n'est indiqué se referer à la description.)

Labelling of vitamin B12 and derivatives thereof through the cyanide nitrogen in  
[CO]-CN

In Anspruch genommene Priorität(en) / Priority(ies) claimed /Priorité(s)  
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LABELLING OF VITAMIN B12 AND DERIVATIVES THEREOF THROUGH THE  
CYANIDE NITROGEN IN [CO]-CN

The invention relates to the derivatization of  
5 vitamin B12 for the labelling with radionuclides, mainly  
 $^{111}\text{In}$ ,  $^{99m}\text{Tc}$  and  $^{131}\text{I}$ . The invention further relates to the  
resulting radiopharmaceuticals and their application as  
radiodiagnostic or radiotherapeutic imaging.

Many patents and publications exists for the  
10 derivatization of vitamin B12 at the corrin ring or the  
ribose moiety.

It was found according to the invention that certain  
metal complexes are able to coordinate directly to the  
cyanide group in vitamin B12. It could be shown that this  
15 type of binding is occurring in particular for the complex  
 $[\text{Tc}(\text{NO})(\text{OH}_2)(\text{CO})_3]$  ( $\text{NO}$  = bidentate ligand) in which the  
nitrogen atom of cyanide binds directly to the Tc metal  
centre forming a  $[\text{Co}]\text{-CN-Tc}$  moiety. It is the first time that  
a metal complex fragment is coordinating to the nitrogen in  
20  $[\text{Co}]\text{-CN}$ .

With the exception of the CN position, all other  
sites in vitamin B12 are exhaustively claimed in patents for  
labelling. To our knowledge, the cyanide is available since  
nobody expected that it can act as a ligand group.

25 The invention thus relates to labeling of vitamin B12  
with  $^{99m}\text{Tc}$  for radiopharmaceutical application in e.g. cancer  
diagnosis and therapy as well as coupling of other metal  
fragments (e.g. Rh, Pt, Pd) to vitamin B12 through the  
cyanide for stereospecific and/or enantioselective catalysis.

30 The reaction of vitamin B12 with low valent metal  
complexes leads to the formation of a stable  $[\text{Co}]\text{-CN-M}$   
bridge. If M is  $^{99m}\text{Tc}$ , this is a convenient method of  
labelling vitamin B12. If M is e.g. Rh(I) the corresponding

complex can probably be used for catalysis since vitamin B12 provides a stereospecific sterical environment. If M is  $^{99m}\text{Tc}$  or  $^{186}\text{Re}$  then the precursor complex is typically [Tc(NO)(OH<sub>2</sub>)(CO)<sub>3</sub>] in which OH<sub>2</sub> is substituted by Co-CN. The ligand NO (or other donor combinations) is variable. This allows a systematic variation of the precursor complex and, thus, a straightforward possibility of product development by systematic structure-activity relationships. A good combination might then represent a labelled B12 derivative, which is either an antagonist or an agonist for B12 receptors and/or transporters.

The ligand NO (or others) can also be bifunctional. One of the functions is used for coordination to the metal and the second function can additionally be coupled to e.g. a targeting vector. This enables combination of receptor targeting, internalization and trapping of labelled vitamin B12. Such a derivative is also called a "trojan horse" if the additional functionality is e.g. enzymatically cleaved inside the cell. It releases then a functionally active or inactive vitamin B12 compound.

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**CLAIM**

1. Method for labeling vitamin B12 with a metal, comprising the reaction of vitamin B12 with a low valent metal complex to obtain a stable [Co]-CN-M bridge.
- 5 2. Method as claimed in claim 1, wherein M is  $^{99m}\text{Tc}$  or  $^{188}\text{Re}$ .
3. Precursor complex having the general formula  $[\text{M}(\text{NO})(\text{OH}_2)(\text{CO})_3]$  in which M is a low valent metal, in particular  $^{99m}\text{Tc}$  or  $^{188}\text{Re}$ ,  $\text{OH}_2$  is substituted by Co-CN and the ligand NO is variable.